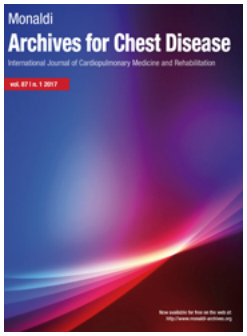

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Nafithromycin: advancements in antibiotic therapy against community-acquired pneumonia-resistant pathogens

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Abstract

Nafithromycin (WCK 4873) is a novel lactone ketolide antibiotic developed to address the critical issue of multidrug-resistant bacteria, especially those causing community-acquired pneumonia (CAP). Given the increasing prevalence of antibiotic resistance, there is a pressing need for new antibiotics with improved efficacy and safety profiles. This review synthesizes data from various *in vitro* studies and clinical trials to evaluate the pharmacological properties, mechanism of action, and clinical potential of nafithromycin. Key clinical trials assessed the drug's pharmacokinetics, safety, and efficacy in both healthy volunteers and patients with CAP. Nafithromycin exhibits strong *in vitro* antimicrobial activity against a broad spectrum of pathogens, including macrolide-resistant and telithromycin-insensitive strains. Clinical trials demonstrated that nafithromycin has a favorable pharmacokinetic profile, with high lung tissue concentrations and manageable side effects. Phase I studies confirmed its safety and tolerability in healthy adults, while Phase II trials showed its efficacy in treating CAP, with a 3-day treatment regimen proving comparable to a seven-day regimen of moxifloxacin.

Nafithromycin holds significant promise as a therapeutic agent against respiratory infections caused by resistant bacteria. Its unique mechanism of action, high tissue penetration, and broad-spectrum activity position it as a valuable addition to the antimicrobial arsenal. Continued research and clinical trials are essential to further define its role in combating antibiotic resistance and ensuring effective treatment options.

Key words: nafithromycin, community-acquired pneumonia, multidrug-resistant bacteria, lactone ketolide antibiotic, pharmacokinetics.

Introduction

Nafithromycin, also identified as WCK 4873, is a novel lactone ketolide antibiotic developed to combat multidrug-resistant bacteria, particularly those causing community-acquired pneumonia (CAP). Its unique chemical structure and mechanism of action make it a promising candidate in the ongoing fight against antibiotic-resistant infections [1].

The rise in antibiotic resistance underscores an urgent need for novel therapeutic agents. Nafithromycin, a macrolide antibiotic, stands out due to its unique structural adaptations, which enhance its pharmacokinetics and antimicrobial effectiveness compared to traditional macrolides like azithromycin [2]. This review delves into its pharmacological features, mechanism of action, and clinical potential. As a macrolide, it shows promise in treating various bacterial infections, including respiratory and skin infections . Its unique structural features and comparative effectiveness against existing antibiotics highlight its therapeutic potential [3].

As a macrolide antibiotic, nafithromycin exhibits significant potential in treating bacterial infections, particularly respiratory and skin infections. It demonstrates robust in vitro activity against a wide range of pathogens, including both typical and atypical bacteria implicated in community-acquired lower respiratory tract infections. Its efficacy has been noted against Streptococcus pneumoniae, with MIC90 values of 0.06 mg/L and activity against macrolide-resistant strains. Other susceptible bacteria include Moraxella catarrhalis, Haemophilus influenzae, Staphylococcus aureus, Mycoplasma pneumoniae, Chlamydophila pneumoniae, and Legionella pneumophila [4].

Class: Antibacterials; Hexoses; Ketolides; Lactones; Macrolides; Pyridines; Thiadiazols

Background on antibiotic resistance

The widespread misuse and overuse of antibiotics have exacerbated the issue of resistance. Pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) and macrolide-resistant *Streptococcus pneumoniae* have highlighted the need for next-generation antibiotics. The CDC has recognized antimicrobial resistance as a severe public health threat, reinforcing the importance of developing agents like nafithromycin to address these challenges [1,5].

Synthesis and chemical properties

The synthesis of nafithromycin involves advanced chiral strategies to ensure high purity and yield. Bhavsar et al. (2023) detailed the development of efficient synthetic routes for

nafithromycin, focusing on the production of the antibiotic with precise chiral properties essential for its biological activity. This research highlights the novel chemical pathways and optimization techniques used to enhance the synthesis process. Its chemical structure ($C_{42}H_{62}N_6O_{11}S$) is shown Figure 1, characterized by a lactone ring and specialized substituents, contributes to its enhanced stability, bioavailability, and resistance to bacterial degradation [6]. These structural innovations support its robust antimicrobial activity and therapeutic potential .

Mechanism of action

Nafithromycin exerts its antibacterial effects by obstructing bacterial protein synthesis. It binds to the 50S ribosomal subunit, preventing the elongation of the peptide chain and thereby disrupting protein synthesis. This mechanism is similar to that of other macrolides but with structural modifications that enhance its activity against resistant bacterial strains. Krokidis et al. (2013) provided insights into the binding interactions of nafithromycin with the ribosomal subunit, explaining its effectiveness in inhibiting protein synthesis [2,7].

The structural modifications in nafithromycin, particularly the lactone ring, enhance its ability to overcome common resistance mechanisms employed by bacteria, such as efflux pumps and ribosomal protection proteins. This makes nafithromycin active against strains that have settled resistance to other macrolides and ketolides. Its ability to inhibit protein synthesis at multiple sites on the ribosome further reduces the likelihood of resistance development [8].

Clinical trials of nafithromycin: phases of clinical trials

Table 1 shows the phases of clinical trials of nafitromycin [9-14].

Nafithromycin, a new lactone ketolide, is being developed for its potential in treating bacterial infections, especially due to its high and lasting concentrations in the lungs. This unique property allows it to effectively combat macrolide-resistant strains of *S. pneumoniae* with a shorter, three-day treatment course. Phase 1 studies in China and ongoing Phase 3 trials in India confirm that nafithromycin achieves significantly higher concentrations in lung tissues compared to plasma, enhancing its ability to kill intracellular bacteria and ensure effective delivery to infection sites [15]. In Phase II trials, nafithromycin demonstrated comparable effectiveness to a seven-day regimen of moxifloxacin for treating community-acquired bacterial pneumonia (CABP), supporting its use in a three-day, once-daily dosing schedule. Its distinct chemical structure contributes to its efficacy and extended lung exposure. Additionally,

nafithromycin has shown promise in reducing inflammation in acute lung injury models, further supporting its therapeutic potential. Its MIC90 of 0.06 mg/L indicates strong activity against resistant strains, aligning with its global efficacy [16].

In vitro activity

Nafithromycin has been shown in numerous studies to have strong in vitro activity against a variety of bacterial pathogens. According to Flamm et al. (2017), it has broad-spectrum activity against modern clinical bacteria, including antibiotic-resistant ones, that were gathered from a global surveillance program. In particular, its effectiveness against Chlamydia pneumoniae, a significant pathogen in respiratory infections, was emphasized by Kohlhoff and Hammerschlag (2021) [8,16,17].

The potential of nafithromycin to treat infections brought on by resistant bacteria is highlighted by these in vitro investigations. It is a versatile antibiotic due to its efficacy against a broad range of pathogens, such as Staphylococcus aureus, Haemophilus influenzae, and Streptococcus pneumoniae. Nafithromycin has the potential to overcome current resistance mechanisms, as evidenced by Zhou et al.'s(2022) demonstration of its activity against isolates of Streptococcus pneumoniae that are resistant to macrolides [18].

Safety and tolerability

The safety and tolerability of nafithromycin have been evaluated in various clinical trials. Iwanowski et al. (2019) reported that nafithromycin is well-tolerated in healthy adult subjects, with minimal adverse effects. Common side effects were mild and included gastrointestinal disturbances, which are typical of macrolide antibiotics [19].

The favorable safety profile of nafithromycin is attributed to its selective targeting of bacterial ribosomes, which reduces the likelihood of off-target effects on human cells. This selectivity is a significant advantage, as it minimizes the risk of adverse reactions and makes nafithromycin suitable for use in a broad range of patients, including those with comorbid conditions [18, 19].

Pharmacokinetics

The pharmacokinetic profile of nafithromycin is characterized by good oral bioavailability, effective plasma concentrations, and favorable distribution in tissues. Iwanowski et al. (2019) conducted studies to assess its safety, tolerability, and pharmacokinetics, revealing that

nafithromycin is well-tolerated in healthy adults with or without food, and maintains therapeutic concentrations over an extended period [19].

Nafithromycin's pharmacokinetics are optimized for treating respiratory infections. Its high tissue penetration, particularly in lung tissues, ensures that effective drug concentrations are achieved at the site of infection. This is crucial for treating pneumonia and other respiratory tract infections. Additionally, its pharmacokinetic properties allow for convenient dosing regimens, which can enhance patient adherence and treatment outcomes [20].

Clinical implications and usage

Nafithromycin has shown significant promise in clinical settings, particularly in the treatment of CAP. Sellarès-Nadal et al. (2020) reviewed investigational drugs for CAP and emphasized the potential role of nafithromycin due to its robust activity against key pathogens and its favorable pharmacokinetic profile[21]. Clinical trials and real-world studies support its use in diverse patient populations, highlighting its efficacy and safety [22].

The Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) have developed guidelines for the management of CAP, which include recommendations for the use of new antibiotics like nafithromycin. These guidelines highlight the need for antibiotics that can effectively treat resistant pathogens and improve patient outcomes. Nafithromycin's broad-spectrum activity and favorable safety profile make it a valuable option for clinicians managing CAP [23].

Resistance mechanisms and overcoming challenges

New antibiotics like nafithromycin must be developed in order to address the growing problem of antibiotic resistance. Solomon and Oliver (2014) discussed the critical threat posed by antibiotic resistance in the United States and the importance of new antibiotics to address this challenge. Nafithromycin is effective against strains resistant to other antibiotics because it has been demonstrated to circumvent common resistance mechanisms like ribosomal protection proteins and efflux pumps [24].

Khande et al. (2017) studied the impact of hyper ermB induction in Streptococcus pneumoniae and Staphylococcus aureus on the activity of nafithromycin, demonstrating its ability to maintain activity against these resistant strains [25]. This highlights the potential of nafithromycin to be used as a frontline treatment for infections caused by multidrug-resistant bacteria.

Comparative studies

Comparative studies have demonstrated the superiority of nafithromycin over existing antibiotics in certain clinical scenarios. Garin et al. (2014) examined the potential advantages of incorporating a macrolide or ketolide, such as nafithromycin, to improve treatment efficacy in moderately severe CAP by contrasting β-lactam monotherapy with β-lactam–macrolide combination treatment.

These comparative studies are essential for establishing nafithromycin's place in clinical practice. By demonstrating its advantages over current treatment options, nafithromycin can be positioned as a preferred choice for treating CAP and other respiratory infections, particularly in settings where resistance to traditional antibiotics is prevalent [26].

Future directions and research

Continued research is essential to fully understand the potential of nafithromycin and its role in treating antibiotic-resistant infections. Future studies should focus on its long-term safety, potential for resistance development, and effectiveness in diverse patient populations. Additionally, exploring its use in combination therapies could further enhance its efficacy and expand its clinical applications [27].

Research should also investigate the potential of nafithromycin to treat other types of infections beyond respiratory tract infections. Given its broad-spectrum activity, it may be useful in treating a range of bacterial infections, such as those of the skin, soft tissues, and perhaps even the gastrointestinal tract [28].

Conclusions

Nafithromycin represents a significant advancement in antibiotic therapy, especially for treating respiratory infections caused by resistant bacteria. It is a promising candidate for clinical use due to its distinct mechanism of action, advantageous pharmacokinetic characteristics, and broad-spectrum activity. Continued research and clinical trials will further define its role in the antimicrobial arsenal and its impact on public health .

The development of nafithromycin underscores the importance of innovation in the field of antibiotic research. As antibiotic resistance continues to pose a significant threat, new antibiotics like nafithromycin are crucial for maintaining effective treatment options and safeguarding public health.

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Table 1. Phases of clinical trials of nafitromycin.

Trial no.	Phase CTID	Study title	Design	Population	Intervention	Explanation	Time frame
1	Phase I NCT02453529	A Phase 1, Multiple-Dose, Open-Label Study to Determine and Compare Plasma and Intrapulmonary Concentrations of WCK 4873 in Healthy Adult Human Subjects	multiple-dose, open-label study	36 healthy adults (18–55 yrs)	WCK 4873 (oral, 3 doses daily)	Plasma and intrapulmonary concentrations of nafithromycin were assessed; 37 AEs (mostly mild, e.g., headaches, dysgeusia). Study confirmed favorable PK and tolerability.[9]	April–July 2015
2	Phase I NCT02770404	A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Safety, Tolerability, and Pharmacokinetic Study of Single-Ascending Doses of Intravenous Nafithromycin in Healthy Adult Subjects	double-blind, randomized, placebo-controlled study	60 healthy adults (18–55 yrs)	IV nafithromycin (100–400 mg) or a placebo with an 8:2 randomization ratio	Safety and PK parameters (AUC, Cmax) were evaluated across ascending doses. Mild AEs confirmed tolerability.[10]	April–December 2016
3	Phase I NCT03926962	Double-Blind, Randomized, Placebo-Controlled Study To Evaluate The Safety, Tolerability And Pharmacokinetics Of Single Ascending Doses And The Effect Of Food On Oral WCK 4873 In Healthy Adult Volunteers		67 healthy adults (18–65yrs)	Oral WCK 4873 (100–1200 mg)	Food impact study showed consistent PK outcomes with no significant safety concerns across doses. Established suitability for oral administration.[11]	March–July 2013
4	Phase I NCT03979859	Double-Blind, Randomized, Placebo-Controlled Study To Evaluate The Safety, Tolerability And Pharmacokinetics Of Multiple Ascending Oral Doses Of WCK 4873 In Healthy Adult Volunteers	randomized, double-blind, single-center, placebo-controlled, sequential cohort study	30 participants (18–55 yrs)	ascending doses of WCK 4873 or placebo once daily under fed conditions for seven days	Evaluated ascending doses under fed conditions. PK data (e.g., AUC, Tmax) confirmed safety and sustained drug absorption.[12]	August–December 2013
5	Phase I NCT03981887	A Phase 1, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Multiple Doses of Intravenous Nafithromycin in Healthy Subjects	randomized, double-blind, placebo-controlled study	10 healthy adults (18–55 yrs)	IV nafithromycin (200 mg BID)	Multiple-dose regimen confirmed favorable PK (high AUC, long half-life) and manageable AEs. Study supported effective systemic delivery via IV route.[13]	June–August 2019
6	Phase II NCT02903836	A Phase II, Randomized, Double-Blind, Multicenter, Comparative Study to Determine the Safety, Tolerability, Pharmacokinetics and Efficacy of Oral Nafithromycin Versus Oral Moxifloxacin in the Treatment of Community-Acquired Bacterial Pneumonia (CABP) in adults	randomized, double-blind study	231 CABP patients (adults)	oral nafithromycin (800 mg every 24 hours for three days) to oral moxifloxacin (400 mg every 24 hours for seven days)	Clinical efficacy comparable to moxifloxacin (7 days) for CABP treatment. Shorter 3-day regimen was effective for symptom resolution, supporting nafithromycin's therapeutic potential.[14]	November 2016–July 2017

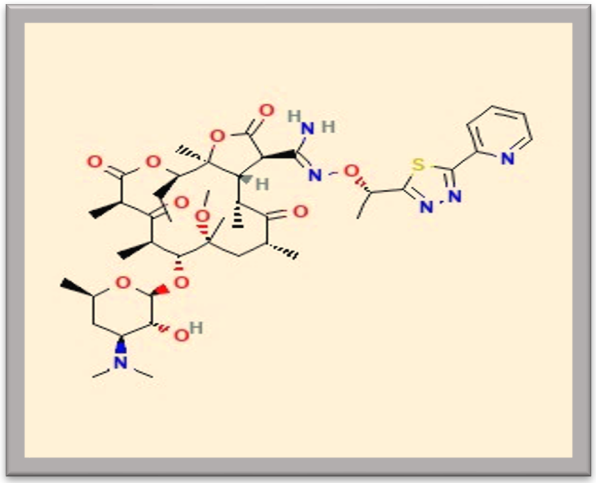

Figure 1. Structure of nafithromycin: C42H62N6O11S. Modified from: National Center for Biotechnology Information, 2025 [5].